Oral Vancomycin Prophylaxis Is Highly Effective in Preventing *Clostridium difficile* Infection in Allogeneic Hematopoietic Cell Transplant Recipients

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Background. *Clostridium difficile* infection (CDI) is a leading cause of infectious complications in allogeneic hematopoietic cell transplant recipients (alloHCT). We sought to evaluate whether prophylactic oral vancomycin reduces the incidence of CDI in alloHCT recipients.

Methods. We conducted a retrospective cohort study to examine the effectiveness of CDI prophylaxis with oral vancomycin, as compared to no prophylaxis, in 145 consecutive adult alloHCT recipients at the University of Pennsylvania between April 2015 and November 2016. Patients received oral vancomycin 125 mg twice daily, starting on admission and continuing until discharge. The primary outcome of interest was the association between oral vancomycin prophylaxis and CDI diagnosis. Secondary outcomes included graft-versus-host disease (GVHD) and relapse.

Results. There were no cases of CDI in patients that received prophylaxis (0/90, 0%), whereas 11/55 (20%) patients who did not receive prophylaxis developed CDI ($P < .001$). Oral vancomycin prophylaxis was not associated with a higher risk of acute, grades 2–4 GVHD (subhazard ratio [sHR] 1.59; 95% confidence interval [CI] 0.88–2.89; $P = .12$), acute, grades 3–4 GVHD (sHR 0.65; 95% CI 0.25–1.66; $P = .36$), or acute, grades 2–4 gastrointestinal GVHD (sHR 1.95; 95% CI 0.93–4.07; $P = .08$) at day 180 post-transplant. No associations between oral vancomycin and relapse or survival were observed.

Conclusions. Prophylaxis with oral vancomycin is highly effective in preventing CDI in alloHCT recipients without increasing the risk of graft-versus-host disease or disease relapse. Further evaluation via a prospective study is warranted.

Keywords. vancomycin; *Clostridium difficile*; stem cell transplant.

Infection remains a major cause of morbidity and mortality following alloHCT [1]. Among the most common infectious complications is *Clostridium difficile* infection (CDI), which occurs in up to 33% of alloHCT recipients and has been identified as an independent risk factor for increased mortality [2, 3]. AlloHCT recipients are particularly susceptible to CDI, owing to a multitude of factors, including extensive exposure to broad-spectrum antibiotics, a prolonged period of neutropenia, lengthy hospitalizations, and gastrointestinal mucosal damage from chemotherapy and/or irradiation [4, 5].

Previous studies have also shown that CDI diagnosis early in the alloHCT course increases the risk of graft-versus-host disease (GVHD), including, specifically, GVHD of the gastrointestinal (GI) tract, an immunologic complication mediated predominantly by donor-derived T cells that react against the recipient's host tissues [6, 7]. The association between CDI and GVHD is alarming, as GVHD is the leading cause of non-relapse mortality in alloHCT recipients [8]. Early CDI during alloHCT has been found to increase the risk of GI GVHD by more than 3-fold [6, 9]. The mechanistic interplay between CDI and GVHD is hypothesized to result from CDI-induced, localized intestinal inflammation, along with a reduction in intestinal microbial diversity. Changes in the intestinal microbiota appear to have significant consequences in the context of alloHCT outcomes, such as GVHD and disease relapse [10].

The high incidence and the potentially severe consequences of CDI in alloHCT recipients highlight the urgently-needed but difficult-to-achieve goal of mitigating the risk of CDI in this patient population. As such, we aimed to evaluate the effectiveness of oral vancomycin prophylaxis in alloHCT recipients, as well

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as to examine the associations between oral vancomycin prophylaxis and other important clinical outcomes, such as GVHD, disease relapse, and survival.

METHODS

We conducted a retrospective cohort study to examine the effectiveness of CDI prophylaxis with oral vancomycin, compared to no prophylaxis, in 145 consecutive adults undergoing alloHCT at the Hospital of the University of Pennsylvania between April 2015 and November 2016. We initiated a pilot program of CDI prophylaxis with oral vancomycin for all alloHCT recipients, starting in December 2015, as a quality-improvement initiative. Patients received oral vancomycin at 125 mg twice daily, starting on the day of inpatient admission for alloHCT and continuing until the day of discharge. Prior to the initiation of this pilot, pharmacologic prophylaxis for CDI was not administered. The primary exposure was receipt of oral vancomycin prophylaxis, which occurred during the time period between December 2015 and November 2016. These exposed patients were compared to unexposed patients between April 2015 and December 2015.

The primary outcome of interest was the association between CDI prophylaxis with oral vancomycin and a diagnosis of CDI during the time from inpatient admission for alloHCT to hospital discharge. *C. difficile* testing on stool samples during the entire study period was performed by the Hospital of the University of Pennsylvania's Clinical Microbiology Laboratory using a commercial enzyme immunoassay for the detection of toxins A and B and glutamate dehydrogenase (C Diff Quik Check Complete, Alere). Samples which were negative for toxins A and B but positive for glutamate dehydrogenase were subsequently tested using polymerase chain reaction (PCR) for toxin genes (BD MAX Cdiff Assay, Becton Dickinson). All alloHCT recipients were admitted to the same inpatient unit, dedicated to the care of HCT patients. All rooms have high-energy particulate air filtration and positive pressure. We are not aware of any practice patterns or changes in cleaning procedures that were made during the study period.

Secondary endpoints included acute, grades 2–4 GVHD; acute, grades 3–4 GVHD; chronic GVHD; relapse; non-relapse mortality (NRM); GVHD-free, relapse-free survival; and overall survival (OS). In addition, the incidence of vancomycin-resistant enterococcus (VRE) bloodstream infections was evaluated, given the previously described association between oral vancomycin exposure and VRE [11]. No routine screening for VRE colonization was performed during the study period. Acute GVHD was graded according to the modified Glucksberg criteria [12]. Chronic GVHD was graded according to the National Institutes of Health Consensus Criteria [13]. Disease relapse was defined as morphological, cytogenetic, or radiological evidence of a disease demonstrating pre-transplant characteristics.

We used the Disease Risk Index stratification system to classify patients according to disease type and status [14].

The following variables were collected using a medical records review: age, sex, disease type, donor source, degree of HLA match, conditioning intensity, disease risk index, CDI history during the prior year, GVHD prophylaxis regimen, and broad-spectrum antibiotic exposure both within 30 days prior to alloHCT and post-transplant until either development of CDI or 30 days after alloHCT, whichever occurred first.

Characteristics were compared between the 2 groups, with categorical variables compared using the χ^2 or Fisher exact test and continuous variables using the Wilcoxon rank-sum test. Primary and secondary outcome analyses were conducted using survival analyses to determine the association between oral vancomycin prophylaxis and the time to development of the event of interest. Time 0 for all outcomes was defined as the date of alloHCT. Acute GVHD outcomes were censored at 6 months for patients who did not reach the event of interest. All other secondary endpoints were censored at 12 months for patients who did not reach the event of interest.

Competing risks regression was used for the GVHD outcomes, relapse, and NRM. For the GVHD and relapse outcomes, death was modeled as a competing risk. For the NRM outcome, relapse was modeled as a competing risk. Subhazard ratios (sHR) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any association. For the outcome of OS, a Cox proportional hazards regression analysis was performed, with the calculation of hazard ratios (HR) and 95% CIs. Potential multivariable models were developed, beginning with the primary exposure of interest: receipt of oral vancomycin prophylaxis. A manual stepwise selection procedure was used, with variables with a *P* value of <.20 on bivariable analysis considered as candidate variables and maintained in the final model if their inclusion was statistically significant on likelihood ratio testing. All calculations were performed using Stata v15.1 (StataCorp LC, College Station, TX). For all calculations, a 2-tailed *P* value <.05 was considered to be significant. This study was approved by the Institutional Review Board of the University of Pennsylvania.

RESULTS

A total of 145 patients were included during the study period, of which 90 (62%) were in the exposed group (ie, received oral vancomycin prophylaxis). An additional 3 patients were unable to receive vancomycin and were excluded from the analysis (2 patients with drug intolerance and 1 patient with a history of vancomycin allergy). Patient and disease-related characteristics are reported in Table 1. Patients were generally high risk by virtue of older age (median 55 years), a high disease risk index score (high/very high: 45.5%), and a hematopoietic cell

Table 1. Patient and Disease Characteristics

Characteristic	Oral Vancomycin Prophylaxis (n = 90)	No Prophylaxis (n = 55)	P Value
Recipient age, in years, median (range)	59 (20–73)	57 (19–72)	.30
Diagnosis, n (%)			.42
Acute myeloid leukemia	47 (52.2)	35 (63.6)	
Acute lymphoblastic leukemia	15 (16.7)	6 (10.9)	
Myelodysplastic syndromes	13 (14.4)	7 (12.7)	
Chronic myeloid leukemia	4 (4.4)	1 (1.8)	
Myelofibrosis	2 (2.2)	2 (3.6)	
Other ^a	9 (10)	4 (7.3)	
Donor source, n (%)			.54
Sibling	27 (30.0)	14 (25.4)	
Unrelated	49 (54.4)	35 (63.6)	
Double umbilical cord blood	8 (8.9)	4 (7.3)	
Haploidentical	6 (6.7)	2 (3.6)	
Conditioning intensity, n (%)			.36
Myeloablative	48 (53.3)	25 (45.5)	
Reduced-intensity	42 (46.7)	30 (54.5)	
Graft source, n (%)			.86
Peripheral blood	58 (64.4)	38 (69.1)	
Bone marrow	24 (26.7)	13 (23.6)	
Double umbilical cord blood	8 (8.9)	4 (7.3)	
GVHD prophylaxis, n (%)			.09
TAC/MTX	59 (65.6)	32 (58.2)	
TAC/MMF	18 (20)	7 (12.7)	
Other ^b	13 (14.4)	16 (29)	
History of <i>Clostridium difficile</i> infection, n (%)	14 (15.6)	5 (9.1)	.32

N = 145.

Abbreviations: GVHD, graft-versus-host disease; MMF, mycophenolate mofetil; MTX, methotrexate; TAC, tacrolimus.

^aOther includes aplastic anemia (n = 1), chronic lymphocytic leukemia (n = 3), Hodgkin's lymphoma CDI (n = 1), multiple myeloma (n = 2), and non-Hodgkin's lymphoma (n = 6).

^bOther includes cyclophosphamide (n = 1), cyclosporine/mycophenolate mofetil (n = 5), tacrolimus/methotrexate/bortezomib (n = 5), tacrolimus/mycophenolate mofetil/cyclophosphamide (n = 10), and tacrolimus/methotrexate/maraviroc (n = 8).

transplantation-specific comorbidity index score (score ≥ 3 : 56.3%).

There were no significant differences in patient, disease, or transplant characteristics between the intervention and control groups. Gram-negative and gram-positive antibiotic exposure within 30 days prior to alloHCT was similar between the groups (Table 2). However, metronidazole use was greater in the control group compared with the intervention group (7% vs 0%;

$P = .02$). There were no differences in the use of gram-negative antibiotics, gram-positive antibiotics, or metronidazole between the intervention and control groups during the time at risk (Table 3).

***Clostridium difficile* Infection**

There were no cases of CDI in patients that received oral vancomycin prophylaxis (0/90; 0%) whereas 11/55 (20%) patients

Table 2. Type of Antibiotic Exposure 30 Days Prior to Allogeneic Hematopoietic Cell Transplantation

Antibiotic	Oral Vancomycin Prophylaxis (n = 90)	No Prophylaxis (n = 55)	P Value
Gram-negative antibiotics, ^a n (%)	17 (19)	9 (16)	.82
Gram-negative antibiotic days, median (IQR)	4 (2, 6) ^b	2 (2, 4) ^b	.57
Intravenous vancomycin, n (%)	7 (8)	6 (11)	.56
Intravenous vancomycin days, median (IQR)	0 (0, 1) ^b	0 (0, 1) ^b	.54
Metronidazole, n (%)	0 (0)	4 (7)	.02
Metronidazole days, median (IQR)	—	1.5 (1, 2)	

Abbreviations: IQR, interquartile range.

^aGram-negative antibiotics included cefepime, piperacillin/tazobactam, meropenem, ceftazidime, aztreonam, and levofloxacin.

^bReported as only including patients who received the antibiotic, given overall low numbers.

Table 3. Type of Antibiotic Exposure Within 30 Days After Allogeneic Hematopoietic Cell Transplantation

Antibiotic	Oral Vancomycin Prophylaxis (N = 90)	No Prophylaxis (N = 55)	P Value
Gram negative antibiotics, ^a n (%)	68 (76)	39 (71)	.54
Gram-negative antibiotic days, median (IQR)	12 (2, 16)	9 (0, 15)	.23
Intravenous vancomycin, n (%)	42 (47)	21 (38)	.32
Intravenous vancomycin days, median (IQR)	0 (0, 4)	0 (0, 6)	.72
Metronidazole, n (%)	6 (7)	9 (16)	.09
Metronidazole days, median (IQR)	3.5 (2, 4)	6 (3, 12)	.053

Time of antibiotic exposure after alloHCT was assessed until either development of CDI or 30 days after transplant, whichever occurred first.

Abbreviations: alloHCT, allogeneic hematopoietic cell transplantation; CDI, *Clostridium difficile* infection; IQR, interquartile range

^aGram-negative antibiotics included cefepime, piperacillin/tazobactam, meropenem, ceftazidime, aztreonam, and levofloxacin.

who did not receive vancomycin prophylaxis developed CDI during alloHCT ($P < .001$). Given the lack of cases in the intervention group, a time-to-event model could not be developed for the primary outcome. The median time to CDI diagnosis was 8 days (interquartile range, 6–12 days) in the control group. The median length of stay was similar between the 2 groups (29 vs. 28 days; $P = .22$). There were 3 patients—1 in the intervention group and 2 in the control group—who developed VRE bloodstream infections during their hospitalizations following alloHCT. There were no differences between the intervention and control groups in the incidences of neutropenic fever (74.4% vs 76.4%, respectively; $P = .80$) or bloodstream infections (21.1% vs 32.7%, respectively; $P = .12$). We also examined the incidence of CDI for 90 days after the completion of oral

vancomycin prophylaxis and found that 4/90 (4.4%) of patients developed CDIs after a median of 60 days (range, 27–83 days) after vancomycin discontinuation.

Graft-versus-Host Disease

The cumulative incidence of acute, grades 2–4 GVHD at day 180 following alloHCT was 39%. In a bivariable analysis, oral vancomycin prophylaxis was not associated with a higher risk of acute, grades 2–4 GVHD (sHR 1.59; 95% CI 0.88–2.89; $P = .12$). In multivariable analyses adjusting for graft sources, the relationship between oral vancomycin prophylaxis and acute, grades 2–4 GVHD remained non-significant ($P = .15$) (Table 4). Similarly, we did not observe an association between acute, grades 3–4 (severe) GVHD by day 180, which occurred

Table 4. Unadjusted Subhazard Ratios for Acute Graft-Versus-Host Disease (GVHD) Outcomes by Day 180 Using Competing Risks Regression With Higher-grade GVHD and Death as Competing Risks

	Acute, Grades 2–4 GVHD, sHR (95% CI)	Acute, Grade, 3–4 GVHD, sHR (95% CI)	Acute, Grades 2–4 GI GVHD, sHR (95% CI)
Oral vancomycin	1.59 (0.88, 2.89); $P = .12$	0.65 (0.25, 1.66); $P = .36$	1.95 (0.93, 4.07); $P = .08$
Age	0.99 (0.97, 1.01); $P = .13$	1.00 (0.96, 1.05); $P = .88$	0.98 (0.96, 1.002); $P = .08$
Female sex	1.14 (0.68, 1.93); $P = .62$	0.56 (0.19, 1.55); $P = .26$	1.39 (0.76, 2.57); $P = .29$
Lymphoid disease	0.67 (0.34, 1.30); $P = .23$	0.71 (0.21, 2.46); $P = .59$	1.09 (0.54, 2.19); $P = .81$
Reduced intensity conditioning	0.66 (0.39, 1.11); $P = .11$	1.44 (0.55, 3.78); $P = .46$	0.65 (0.35, 1.20); $P = .17$
Donor source ^a			
Unrelated	1.48 (0.77, 2.86); $P = .24$	0.75 (0.25, 2.29); $P = .62$	1.27 (0.59, 2.77); $P = .54$
Other	1.84 (0.74, 4.57); $P = .19$	1.81 (0.47, 7.01); $P = .39$	2.18 (0.80, 5.96); $P = .13$
HLA match ^b			
9/10	1.35 (0.24, 7.67); $P = .73$	5.89 (1.04, 33.4); $P = .045$	2.11 (0.37, 12.1); $P = .41$
Other	1.53 (0.72, 3.27); $P = .27$	2.49 (0.77, 8.02); $P = .13$	2.03 (0.89, 4.61); $P = .09$
HCT type ^c			
Bone marrow	0.85 (0.44, 1.64); $P = .63$	0.78 (0.22, 2.81); $P = .70$	0.62 (0.28, 1.38); $P = .24$
Cord	2.76 (1.18, 6.43); $P = .02$	4.13 (1.22, 13.9); $P = .02$	3.11 (1.23, 7.86); $P = .02$
GVHD prophylaxis regimen ^d			
TAC/MMF	1.46 (0.75, 2.84); $P = .27$	1.02 (0.28, 3.64); $P = .98$	1.77 (0.83, 3.77); $P = .14$
Other	0.82 (0.39, 1.75); $P = .61$	0.90 (0.24, 3.33); $P = .87$	0.78 (0.31, 1.94); $P = .59$

Abbreviations: CI, confidence interval; GI, gastrointestinal; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; MMF, mycophenolate mofetil; sHR, subhazard ratio; TAC, tacrolimus.

^aReference is the related donor.

^bReference is the 10/10 HLA-match.

^cReference is the peripheral blood stem cell source.

^dReference is tacrolimus/methotrexate.

in 12% of the overall cohort, and oral vancomycin prophylaxis (sHR 0.65; 95% CI 0.25–1.66; $P = .36$).

As an exploratory analysis, we then examined the relationship between oral vancomycin prophylaxis and risk of any acute, grades 2–4 GVHD that involved the GI tract by day 180 post-alloHCT. The cumulative incidence of acute, grades 2–4 GI GVHD was 28%. There was a trend towards a higher incidence of acute, grades 2–4 GI GVHD in the intervention group, but this association did not reach statistical significance (sHR 1.95; 95% CI 0.93–4.07; $P = .08$). Similar analyses were conducted for chronic GVHD at 1 year post-alloHCT, and no associations were identified (sHR 1.70; 95% CI 0.53–5.36; $P = .36$).

We repeated similar analyses for the risk of acute GVHD occurring by day 100. The cumulative incidence of acute, grades 2–4 GVHD at day 100 was 25%. Oral vancomycin prophylaxis was not associated with a risk of acute, grades 2–4 GVHD at day 100 (sHR 1.26; 95% CI 0.63–2.53; $P = .52$). We also examined the association between oral vancomycin exposure and acute, grades 3–4 GVHD. The cumulative incidence of acute, grades 3–4 GVHD at day 100 was 7.6%. On multivariable analysis, when adjusting for graft source, oral vancomycin was associated with a reduced risk of acute, grades 3–4 GVHD at day 100 (sHR 0.27; 95% CI 0.08–0.94; $P = .04$).

Relapse

Because alterations in the intestinal microbiota have been associated with mitigation of the graft-versus-tumor effect, we sought to evaluate whether oral vancomycin prophylaxis influenced a risk of disease relapse. The cumulative incidence of disease relapse was 28% at 1 year post-alloHCT. In a bivariable analysis, oral vancomycin prophylaxis was not associated with an increased risk of disease relapse (sHR 0.80; 95% CI 0.43–1.50; $P = .50$). In a multivariable analysis, adjusting for sex, there was no significant difference in the risk of relapse between groups.

Non-relapse Mortality; Graft-versus-Host Disease-free, Relapse-free Survival; and Overall Survival

The 1-year estimated rate of OS was 72%. Vancomycin prophylaxis was not associated with OS (HR 0.60; 95% CI 0.32–1.12; $P = .11$) or NRM (HR 0.72; 95% CI 0.29–1.83; $P = .49$). There was no significant difference in GVHD-free, relapse-free survival rates between control and intervention patients (38.2% vs. 45.6%, respectively; $P = .39$) at 1 year.

DISCUSSION

We demonstrated that oral vancomycin prophylaxis was highly effective in preventing CDI in alloHCT recipients, as no patient that received the intervention developed CDI, compared to a 20% CDI rate in the control group. Oral vancomycin prophylaxis was not associated with an increased risk of GVHD or disease relapse. Moreover, oral vancomycin prophylaxis did not result in an increase in VRE bloodstream infections. To the best

of our knowledge, this study is the first to examine the clinical benefit of primary prophylaxis with oral vancomycin against CDI in alloHCT recipients.

Risk factors for CDI in alloHCT recipients include a prior history of CDI, myeloablative conditioning, broad-spectrum antimicrobial use, and an age greater than 60 years [15–20]. Unfortunately, the majority of CDI risk factors in the alloHCT population are not modifiable. Thus, the high incidence rate and lack of modifiable predisposing factors has created an urgent need to identify novel strategies to mitigate the risk of this infectious complication. We opted to initiate oral vancomycin prophylaxis on admission for a transplant, as the majority of CDI cases are diagnosed early in the alloHCT course. In our institution, the median time to CDI diagnosis was 8 days from admission for alloHCT, which is consistent with previous findings [16, 19]. While we did not perform a medical records review to differentiate whether a PCR-positive test was suggestive of infection versus colonization, previous data from our institution suggest that hematologic malignancy patients with enzyme immunoassay-positive and PCR-positive tests have similar rates of signs and symptoms of infections and clinical outcomes [21].

The effectiveness of oral vancomycin for CDI prevention has been previously examined as a secondary prophylaxis approach in non-oncology settings, with encouraging findings [22–24]. However, these analyses did not include alloHCT recipients, who have a higher risk of CDI, and, thus, the results from the non-oncology setting are not generalizable. In addition, the existing literature has examined the effectiveness of oral vancomycin as a secondary prophylaxis against CDI, whereas in our study, the majority of patients were treated with oral vancomycin for primary prophylaxis. Recently, a randomized, placebo-controlled trial evaluated the role of fidaxomicin for the prevention of CDI in alloHCT recipients receiving fluoroquinolone prophylaxis and found similar prophylaxis failure rates between the 2 arms, but fewer confirmed CDI diagnoses with fidaxomicin [25]. These findings are encouraging, although a comparison of the efficacy and safety of fidaxomicin and oral vancomycin for this specific indication is not available.

We also examined whether oral vancomycin prophylaxis influenced the risk of immune-mediated processes such as GVHD and disease relapse, given the recently-described associations between a loss of intestinal microbial diversity and alloHCT clinical outcomes [26, 27]. We did not identify an association between oral vancomycin prophylaxis and either acute GVHD at 180 days post-alloHCT or chronic GVHD at 1 year post-alloHCT. Of note, oral vancomycin was protective against severe, acute GVHD occurring by day 100, but not by day 180. The associations between oral vancomycin prophylaxis and severe, acute GVHD remain an important area for future study. In addition, we also observed a trend towards a higher incidence of acute, grades 2–4 GVHD of the GI tract in

the intervention arm, but these data did not achieve statistical significance. The lack of association between oral vancomycin exposure and an increased risk of GVHD is noteworthy, given recent findings from several groups that have suggested that the classes of antimicrobials that are administered to alloHCT recipients may impact the risk of GVHD via effects on commensal bacteria [28, 29]. In addition, a retrospective analysis of 857 alloHCT recipients concluded there was a higher risk of GVHD-related mortality in patients who were treated with either imipenem-cilastatin or piperacillin-tazobactam for neutropenic fever. Interestingly, the authors of this analysis did not observe a relationship between oral vancomycin exposure and GVHD-related mortality [26]. Another retrospective examination of 399 alloHCT recipients reported a higher risk of GI GVHD in patients exposed to penicillin derivatives and carbapenems [30].

The nexus between CDI, oral vancomycin, and GVHD is poorly characterized and is a very active area of research, given transplant recipients' susceptibility to intestinal dysbiosis from extensive exposure to systemic antibiotics, cytotoxic chemotherapy, and irradiation [10]. Several studies in non-oncology settings have found that oral vancomycin reduces microbial diversity via a decrease in gram-positive bacteria, as well as the gram-negative, anaerobic *Bacteroides* species [31–33]. However, the effects of oral vancomycin on intestinal microbial diversity in the context of an alloHCT have not been examined, and the understanding of what interconnection exists between oral vancomycin, intestinal microbiome integrity, and GVHD remains scant. Further complicating matters related to the microbiome in the context of HCT is the role of prophylactic gut decontamination, a strategy that many transplant centers continue to practice in an effort to reduce GVHD [34]. Early data suggested a reduction in GVHD with gut decontamination, but more recent evidence has shown this strategy may actually increase the risk of GVHD [35–37]. Oral vancomycin is a drug that often comprises part of the pharmacologic gut decontamination process, and how its presence affects the outcomes of gut decontamination remains unknown. Consequently, our center does not utilize gut decontamination as a GVHD reduction strategy: a recommendation consistent with consensus guidelines [38].

In our study, we did not observe an association between oral vancomycin prophylaxis and disease relapse, implying that oral vancomycin does not impair the graft-versus-tumor effect, although this was an observational study that was not powered to detect relapse differences. Nevertheless, this is an important finding given the results of a recent retrospective study that demonstrated an inverse correlation between the anaerobic, gram-positive rod *Eubacterium limosum* and the risk of disease relapse in alloHCT recipients [27]. The associations between intestinal microbiome integrity and the graft-versus-tumor effect remain to be determined.

There are several limitations to this analysis. AlloHCT recipients rarely receive homogeneous antibiotic therapy, which makes it challenging to robustly evaluate the effects of oral vancomycin on immune-mediated processes, such as GVHD and disease relapse, in the context of heterogeneous antimicrobial exposure. That being said, we did not identify any differences in gram-negative or gram-positive antibiotic exposure within 30 days prior to or during the time at risk after alloHCT between the 2 arms. Interestingly, more patients in the control arm received metronidazole, an active agent against CDI, prior to alloHCT. Despite a higher use of metronidazole in the control arm, the incidence of CDI was higher in this group. In addition, this was a retrospective study of sequential rather than concurrent patients. However, we could not identify any changes in our clinical practice during the time period other than the use of oral vancomycin prophylaxis for all alloHCT that may have influenced CDI rates. Also, the sample size in this study was relatively small and may not have been powered to detect differences in more rare outcomes. Moreover, the lack of difference in the length of hospitalization, incidence of GVHD, and survival outcomes between the 2 groups raises the argument of whether treating CDI early may not be worse than preventing its occurrence. Long-term follow-up in a larger number of patients will be critical to address this quandary, particularly for the latter 2 endpoints.

In summary, prophylaxis with oral vancomycin is highly effective in preventing CDI in alloHCT recipients without increasing the risk of GVHD or disease relapse. Detailed evaluation via a prospective protocol is warranted.

Notes

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